Molecular Mechanics-Based Measures of Steric Effects: Customized Code to Compute Ligand Repulsive Energies

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ABSTRACT: Ligand repulsive energies, E_R, have been demonstrated to provide reliable steric parameters for ligands in organometallic systems. To date, ligand repulsive energies have been computed manually using commercially available molecular mechanics code. We report a customized code, *ERCODE*, that calculates ligand repulsive energies. Some reported E_R values differ from those in the literature due to a modified conformational search strategy presented. Updated ligand repulsive energies for 100 phosphines, 12 phosphites, 26 amines, and 54 alcohols, ethers, and sulfides are presented.
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Introduction

Quantification of the steric properties of a ligand has been an important theme in chemistry for over 100 years. Most importantly, the steric properties of ligands have been used to correlate with kinetic and thermodynamic variables in linear free-energy relationships (LFER).[1] In inorganic and organometallic chemistry, there are three popular quantitative measures of the steric effect of a ligand: Tolman's cone angle, θ,[2] solid angles, Ω,[3] and Brown's ligand repulsive energy, E_R.[4] Each of these measures is associated with advantages and disadvantages and the topic of general ligand steric properties has been the subject of three reviews.[5–7]

Ligand repulsive energies were originally developed to quantify the steric influence of P- and As-donor ligands in a prototypical $Cr(CO)_5$ environment.[4] To calculate the E_R value for a ligand, L, a good representation of the lowest energy conformation of the $Cr(CO)_5L$ complex was first obtained using Cerius^2, a comprehensive molecular modeling suite produced by Molecular Simulations Inc.[8] Originally, a modified MMP2 force field[9]

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was used.[4, 10, 11] Once the best representation of the global minimum conformation was determined, the equilibrium Cr—L bond distance, r_e, was calculated. To separate electronic from steric effects, the van der Waals equation was changed from the Buckingham potential,

$$E = D_0\left\{\left(\frac{6}{\gamma-6}\right)\exp\left[\gamma\left(1-\frac{R}{R_0}\right)\right] - \left(\frac{6}{\gamma-6}\right)\left(\frac{R_0}{R}\right)^6\right\} \quad (1)$$

(D_0 is the geometric mean of the potential well depths, γ is a scaling factor, R is the interatomic distance, and R_0 is the arithmetic mean of the van der Waals radii), to the pure repulsive potential,

$$E_{vdW,R} = D_0 \exp\left\{\gamma\left(1-\frac{R}{R_0}\right)\right\}. \quad (2)$$

With all other internal coordinates of the molecule frozen, the van der Waals repulsive energy was calculated as a function of Cr—L bond distance. In the limit of the small distances employed in the calculation, the plot of $E_{vdW,R}$ vs. distance is linear.[4] Ligand repulsive energy was defined as the negative slope of the $E_{vdW,R}$ vs. distance plot scaled by r_e:

$$E_R = -r_e\left(\frac{\partial E_{vdW,R}}{\partial r}\right). \quad (3)$$

Since its definition, ligand repulsive energies have been calculated for P-, As-,[4] N-,[12] S-, and O-donor ligands,[13] η^2-bonded olefins,[14] and organic substituents.[15] In addition to the $Cr(CO)_5$ fragment, [(η^5—C_5H_5)Rh(CO)],[16] CH_2COOH, and CH_3[15] have been used as prototypical fragments. Plots of E_R [$Cr(CO)_5$ fragment] vs. E'_R (other fragments) are linear, demonstrating the versatility of the measure. Finally, we have shown that ligand repulsive energies computed from structures minimized in the modified MMP2 force field[9] are linearly related to those calculated using Rappé's[17] universal force field.[15]

In this article, we present a customized piece of code, *ERCODE*, which calculates ligand repulsive energies using the same methodology developed by Brown.[4] *ERCODE* enables rapid and reliable calculation of ligand repulsive energy values from any bgf file for a molecular system. Ligand repulsive energies generated using *ERCODE* are compared with literature values for E_R,[4, 12, 13] and an updated set of ligand repulsive energy data is presented. The literature values for E_R were computed manually: van der Waals repulsive energies were calculated using molecular mechanics and the slope of the plot of van der Waals repulsive energy vs. distance calculated using a standard spreadsheet. Details of the comparison between E_R values published in the literature, and those presented in this work are discussed below.

ERCODE Program

ERCODE begins by setting up a reference list, called rlist[][]; a two-dimensional character array that stores van der Waals constants R_0 and D_0 [eq. (2)] for each atom type in the molecule. We keep a parameter file, called param_r.set, external to the code to allow the user to readily modify the variables defined in eq. (2). By default, the parameters listed in param_r.set are supplied with the Cerius[2] code[8] and are consistent with the MMP2[9] or universal force fields.[17] *ERCODE* then prompts the user for an output filename: if an existing filename is specified, the file will be overwritten. Because *ERCODE* is a DOS-based program, an 8.3 file name must be specified. If longer file names are used, they will be truncated with ~1.

To begin the calculation, the user is prompted for a bgf file name that contains the name of the complex of interest. Again, the DOS-based 8.3 convention is required. We use bgf files in this study because they have all force field atom-type information conveniently stored along with connectivity data that is easy to extract. Other structural file types can be converted into bgf file types using available code, for example, Cerius[2] or Babel. For each atom in the bgf file, *ERCODE* stores the atom number, the *x*-, *y*-, and *z*-coordinates, and the force field atom type in a linked list. At this point in the linked list each atom has one node containing five fields associated with it. In addition, each node of the link list has three additional fields: R_0, D_0, and side values, defined below. The R_0 and D_0 values are then extracted from param_r.set for each atom and stored in the linked list. If *ERCODE* cannot find a particular R_0 or D_0 value in the parameter file, it prompts the user to enter appropriate numbers. *ERCODE* then works with the connectivity table.

Because we are only interested in nonbonded interactions, it is essential that any bonded interactions be excluded in the calculation of the van der Waals repulsive energy. In *ERCODE*, atom connectivity information is stored in a two-dimensional integer array called cons[][]. The array cons[0] contains the list of atom numbers to which atom 1 is connected. Similarly, cons[1] lists the atoms connected to atom 2, etc. Each integer array is terminated with −1. Because we are only interested in

nonbonded interactions, *ERCODE* must exclude all interactions between atoms that are in a 1–2 or 1–3 relationship, consistent with the protocols for the MMP2 type of force field.[9] To achieve this, *ERCODE* implements a two-dimensional binary array, called m[][]. As with cons[][], m[][] is stored consecutively so that m[0] is the binary array associated with the first atom. This means that for two atoms x and y, the binary array is listed as m[$x-1$][$y-1$]. An entry of zero in m[$x-1$][$y-1$] indicates that the two atoms x and y are in a 1–2 or 1–3 relationship. An entry of one in the array indicates that the two atoms are in a nonbonded relationship and need to be included in the calculation of van der Waals repulsive energy [eq. (2)]. When *ERCODE* is executed, every element of the array is initialized, terminating with a -1. *ERCODE* then determines which atoms are connected to the atom of current interest using cons[][] and a series of highly nested statements. Because we only want to calculate the van der Waals repulsive energy between a pair of atoms once, *ERCODE* adjusts the binary array so that if there is a one at m[3][6], for example, there will be a zero at m[6][3]. At the end of this process, all the pairs of atoms that are to be used in eq. (2) have entries of one in the m[][] array.

Ligand repulsive energy is defined in terms of the change in the van der Waals repulsive energy with distance [eq. (3)].[4] This means that the ligand–fragment distance needs to be varied in the calculation of E_R. To adjust the ligand–fragment distance, *ERCODE* must determine which atoms are on the ligand side of the molecule and which are on the fragment side. The user supplies the atom numbers for the metal and ligand donor atom, which are used to define the fragment and ligand, respectively. Although we report on $Cr(CO)_5L$ complexes in this article, *ERCODE* is not confined to any particular fragment or ligand, provided the necessary van der Waals paramters are defined in param_r.set. *ERCODE* requires the user to identify atom numbers that represent the anchoring position for prototypical fragment and donor atom attached to this anchoring position. We have already used *ERCODE* to report E_R and E'_R values for a variety of organic substituents using $Cr(CO)_5$, CH_3, and CH_2COOH fragments.[15] [We reserve the label E_R to refer to the prototypical $Cr(CO)_5$ fragment to be consistent with the work of Brown. For all other fragments, we call the ligand repulsive engery E_R (fragment).] In the linked list mentioned above, a side field is used to identify an atom as being on the ligand or fragment side of the molecule. This side parameter for each atom is implemented as a one-dimensional array called side_array. Each element of the side_array is dedicated to one atom in the molecule, and is indexed by the atom number. If the atom is on the ligand side of the molecule, we enter a 1 in the side field. When *ERCODE* is first run, every element of the side_array is set to -1. Then *ERCODE* assigns a zero to the ligand donor atom number, and all atom numbers numbers on the ligand side of the molecule by recursively traversing through the cons[][] array. Once complete, all of the atom numbers that were on the ligand side of the molecule have a zero in their corresponding location in the side_array. *ERCODE* then assigns a value of one to the metal atom, which was identified by the user. Then the atoms on the fragment side of the molecule are identified. *ERCODE* changes all side_array[] values of -1 to 1, indicating that the atoms are on the fragment side of the molecule. This completes the filling of the side_array. All that remains is to transfer these data to the nodes of the linked list. *ERCODE* traverses the linked list and the side_array simultaneously to set the side element in each node of the corresponding atom. Finally, *ERCODE* calculates the distance between donor atom and metal, r_e, and defines the unit vector between them. (This vector will allow us to move the fragment with respect to the ligand in the calculation of E_R.)

In the original MM2 code, Allinger instituted a CH shrink feature,[9] and, by default, a factor of 0.915 was used. *ERCODE* allows the user to decide whether or not to implement this CH shrink. If CH shrink is used, *ERCODE* traverses the linked list looking for H__C force field types. When these hydrogens are found, the distance between the C and H is calculated, and multiplied by 0.915. A new set of coordinates for the H is calculated and the H atom moved to the new position.

According to eq. (3), ligand repulsive energy, E_R, is the slope of the plot of van der Waals repulsive energy against metal–ligand distance. (This plot is linear for the small distances by which the metal–ligand bond is varied.) To calculate this slope, we compute the van der Waals repulsive energy for the molecule at seven different metal–ligand distances: three at distances longer than r_e (each by 0.01 Å), three at distances shorter than r_e (each by 0.01 Å), and one at r_e. We apply eq. (2) to the pairs of atoms identified in the binary array m[][]. *ERCODE* reads m[][] in search of ones, and prepares to calculate the seven van der Waals repulsive energies per pair of atoms using eq. (2). In other words, we keep seven running totals of van der Waals repulsive energies for each pair of atoms. To use eq. (2), we need to extract R_0 and D_0 values for each atom in the pair

identified by m[][]. In the implementation of eq. (2), we use the geometric mean of D_0 and arithmetic mean of R_0 values. At this point *ERCODE* calls the function vander, which calculates van der Waals repulsive energies.

When the vander function is called, the side field becomes very important because we need to move the fragment with respect to the ligand [eq. (3)]. However, we do not want to change the atomic coordinates in the original bgf file, so we create a temporary coordinate variable to hold the atomic coordinates. If side_array[] = 1, we calculate a set of scaled coordinates by multiplying the distance factor by the unit vector along the metal–ligand bond length. The distance factor is the distance by which the fragment atoms are moved, in the direction of the metal–ligand bond, towards the ligand. If side_array[] = 0, then the atom is not moved. At this point, all variables in eq. (2) are defined with the exception of R, the distance between the atoms, which is calculated from the atomic coordinates using the distance formula.

With all seven van der Waals repulsive energies, we are in a position to calculate E_R according to eq. (3). We calculate the slope, m, from the van der Waals repulsive energy and distance data according to eq. (4),

$$m = \frac{S_{xy}}{S_{xx}}, \tag{4}$$

where

$$S_{xy} = \sum x_i^2 y_i^2 - \frac{\sum x_i \sum y_i}{7}, \qquad S_{xx} = \sum x_i^2 - \frac{(\sum x_i)^2}{7}. \tag{5}$$

[x_i is the distance, r, in eq. (3) and y_i is the van der Waals repulsive energy.] The slope, m, is multiplied by r_e [eq. (3)], and the result sent to the user-defined output file along with the bgf file name.

Once completed, *ERCODE* frees memory used up by the linked list and closes the input file. *ERCODE* then prompts the user for another filename and the process is repeated. To terminate the program, the user enters an invalid filename and is returned to the main menu. When *ERCODE* exits, the output file is closed.

Where to Obtain *ERCODE*

ERCODE is written in C++. The source code, ercode.cpp, is supplied as supplementary material. Ordering information is available on any current masthead. Executable copies of the code are available from the corresponding author.

Results and Discussion

All molecular mechanics calculations were carried out on a Silicon Graphics O[2] R12000 workstation. Molecular modeling was carried out using Cerius[2] version 4.0[8] using the MMP2 force field,[9] with modifications listed in earlier publications.[10–13, 15, 16] Structure files were saved in the bgf file format and transferred to a 500 MHz Pentium III PC operating under Windows 98. On the PC, the files were submitted to *ERCODE* for ligand repulsive energy calculation.

Ligand-repulsive energies were computed for a variety of P-, N-, S-, and O-donor ligands, L (Table I). The new set of E_R values represents the most reliable values available; using the energy minimized structures based on extensive minimization and conformational searching routines. The $Cr(CO)_5L$ complexes were built in Cerius[2] 4.0 and then energy minimized (SMART minimizer, maximum of 500 steps of minimization, termination criterion of 0.100 kcal/mol·Å). The complexes were then subjected to a Monte Carlo conformational search in which the torsion angles for all the rotatable bonds were allowed to vary simultaneously by randomly different amounts and each structure energy minimized (SMART minimizer, maximum of 500 steps of minimization, termination criterion of 0.100 kcal/mol·Å). Usually, the Monte Carlo search generated 2000 structures of which the lowest in energy was selected and fully energy minimized (SMART minimizer, maximum of 5000 steps, termination criterion of 0.0100 kcal/mol·Å). This refined minimum energy structure was submitted to *ERCODE* for the calculation of E_R.

Ligand-repulsive energies computed using *ERCODE* were compared to hand calculations to check for errors in the program. The values from *ERCODE* were essentially identical to the ligand-repulsive energies calculated by hand using the literature method. *ERCODE* ligand-repulsive energies were then compared to literature values for E_R.[4, 12, 13] A plot of E_R (from *ERCODE*) vs. literature ligand repulsive energy, E_R,[4, 12, 13] for the entire set of ligands was generated (Fig. 1). Linear regression analysis using the least-squares method was performed on each set of ligands (phosphines, phosphites, amines, and O- and S-donors) separately, and showed excellent correlations (r = 0.91–0.99). Ligands with few conformational degrees of freedom give E_R values from *ERCODE* that are almost identical to the values reported in the literature. However, we noted greater deviations

TABLE I.

Ligand Repulsive Energies (kcal/mol) Computed Using *ERCODE* for a Variety of Phosphines, Phosphites, Amines, O-, and S-Donor Ligands.

Phosphines		$PMeEt(i\text{-}Pr)$	62	$P(OPh)_3$	66
PH_3	10	$P(n\text{-}Pr)_3$	62	$P(O\text{-}i\text{-}Pr)_3$	68
PH_2Me	18	$P(CH_2CH_2CN)_3$	63	$P(O\text{-}i\text{-}Pr)_2(O\text{-}t\text{-}Bu)$	70
PH_2Et	19	$P(n\text{-}Bu)_3$	63	$PPh_2(OEt)$	70
PH_2CH_2Bn[a]	19	PPh_2Et	65	$P(O\text{-}i\text{-}Pr)(O\text{-}t\text{-}Bu)_2$	82
$PH_2(n\text{-}Pr)$	19	$PMe_2(t\text{-}Bu)$	66	$P(O\text{-}t\text{-}Bu)_3$	95
$PH_2(n\text{-pentyl})$	19	$PPh_2(n\text{-}Bu)$	66	**Amines**	
$PH_2(CH_2\text{-}i\text{-}Bu)$	20	PCy_3[b]	66	NH_3	9.2
$PH_2(CH_2\text{-}i\text{-}Pr)$	20	$PPh_2(i\text{-}Bu)$	70	NH_2Me	31
$PH_2(CH_2\text{-}t\text{-}Bu)$	21	$PMe(i\text{-}Pr)_2$	72	NH_2Et	32
PH_2Ph	22	$P(p\text{-anisyl})_3$	73	$NH_2(n\text{-}Pr)$	32
$PH_2(i\text{-}Pr)$	26	$PEt_2(i\text{-}Pr)$	74	$NH_2(i\text{-}Bu)$	33
$PH_2(o\text{-tolyl})$	26	$P(p\text{-tolyl})_3$	74	$NH_2(\text{neopentyl})$	34
$PH_2(s\text{-}Bu)$	27	$P(p\text{-}C_6H_4F)_3$	74	$NH_2(i\text{-}Pr)$	40
$PPhMe_2$	28	$P(m\text{-}C_6H_4F)_3$	74	$NH_2(s\text{-}Bu)$	42
$P(CH_2)_3Ph$	30	PPh_3	74	NH_2Cy[b]	42
PHMePh	30	$PMe(CH_2\text{-}t\text{-}Bu)_2$	74	$NH_2(\text{adamantyl})$	44
PH_2Bn[a]	32	$P(m\text{-}C_6H_4Cl)_3$	74	$NH_2(t\text{-}Bu)$	50
$PHMe(CH_2\text{-}t\text{-}Bu)$	32	$P(p\text{-}C_6H_4Cl)_3$	74	$NHMe_2$	60
PHEtPh	32	$PPhCy_2$[b]	75	Piperidine	64
$PH_2(t\text{-}Bu)$	33	PPh_2Et	75	NHMeEt	65
PH_2Cy[b]	33	$PPh_2(i\text{-}Pr)$	75	$NHEt_2$	73
$PH_2(\text{xylyl})$	34	$P(m\text{-tolyl})_3$	76	$NH(n\text{-}Pr)_2$	75
PHMeEt	34	$P(m\text{-}C_6H_4\text{-}t\text{-}Bu)_3$	76	NMe_2Et	85
$PH_2(\text{mesityl})$	34	PPh_2Cy[b]	77	$NH(i\text{-}Bu)_2$	89
$PHMe(n\text{-}Pr)$	35	PBn_3[a]	85	$NH(s\text{-}Bu)_2$	91
$PHMe(n\text{-}Bu)$	36	$PH(t\text{-}Bu)_2$	86	$NMeEt_2$	94
$PHMe(i\text{-}Pr)$	37	$PEt(i\text{-}Pr)_2$	87	NMe_3	97
$PH(n\text{-}Pr)_2$	38	PPh_2Bn[a]	88	$NH(i\text{-}Pr)_2$	107
$PHEt_2$	38	$PEt_2(t\text{-}Bu)$	90	NEt_3	111
$PHPh_2$	38	$P(t\text{-}Bu)_2Et$	93	$NHCy_2$[b]	115
PMe_3	38	$PMe(i\text{-}Pr)_2$	93	$N(n\text{-}Pr)_3$	116
$PH(n\text{-}Bu)_2$	38	$PPh(t\text{-}Bu)_2$	95	$N(i\text{-}Pr)_3$	176
$PHEt(n\text{-}Pr)$	39	$PPh_2(t\text{-}Bu)$	95	**O-Donor Ligands**	
$PHEt(n\text{-}Bu)$	39	$P(\text{menthyl})_2(i\text{-}Pr)$	97	H_2O	6.8
PMe_2Et	42	$P(i\text{-}Bu)_3$	100	MeOH	24
PMe_2Ph	43	$P(i\text{-}Pr)_2(t\text{-}Bu)$	102	EtOH	32
$PHEt(i\text{-}Pr)$	44	$PEt(i\text{-}Pr)(t\text{-}Bu)$	106	n-PrOH	35
$PH(i\text{-}Bu)_2$	45	$P(t\text{-}Bu)_2(i\text{-}Pr)$	107	Me_2O	37
PHMeBn[a]	45	$P(i\text{-}Pr)_3$	107	THF	51
$PHMe(t\text{-}Bu)$	47	$P(t\text{-}Bu)_2Et$	107	$MeO(n\text{-}Pr)$	64
$PMe_2(CH_2\text{-}t\text{-}Bu)$	51	$P(\text{neopentyl})_3$	108	MeOEt	65
$PMeEt_2$	52	$P(s\text{-}Bu)_3$	109	$n\text{-}Pr_2O$	65
$PMe_2(i\text{-}Pr)$	52	$P(t\text{-}Bu)_2Me$	112	$n\text{-}Bu_2O$	67
$PPhEt_2$	54	$P(o\text{-tolyl})_3$	112	Et_2O	68
$PH(CH_2\text{-}t\text{-}Bu)_2$	55	$P(t\text{-}Bu)_3$	134	$EtO(n\text{-}Pr)$	70
$PHCy_2$[b]	55	$P(\text{mesityl})_3$	155	$MeO(t\text{-}Bu)$	76
$PPh(n\text{-}Bu)_2$	56	**Phosphites**		**Sulfides**	
$PMePh_2$	57	$P(OCH_2)_3CCH_3$	21	SMe_2	43
$PH(i\text{-}Pr)(t\text{-}Bu)$	58	$P(OMe)_3$	52	$SMe(s\text{-}Bu)$	46
$PH(i\text{-}Pr)_2$	59	$P(O\text{-}n\text{-}Bu)_3$	52	SBn_2[a]	49
$PHEt(t\text{-}Bu)$	59	$P(OEt)_3$	53	SMeEt	49
PEt_3	60	$PPh_2(OMe)$	65	$SMe(n\text{-}Bu)$	51
PPh_2Et	61	$PPh(OMe)_2$	65	$SMe(n\text{-}Pr)$	51

TABLE I.
(Continued)

SMe(*i*-Bu)	52	S(*s*-Bu)$_2$	59	SEt(*t*-Bu)	66
SEt(*i*-Pr)	53	SEt(*n*-Pr)	60	S(*i*-Pr)$_2$	66
SEt(*s*-Bu)	53	SEt(*n*-Bu)	61	SEtBn[a]	67
SMe(*i*-Pr)	53	SEt(*i*-Bu)	62	S(*n*-Pr)(*t*-Bu)	68
S(*n*-Pr)(*i*-Pr)	54	S(*n*-Pr)$_2$	62	S(*i*-Bu)Bn[a]	69
S(*n*-Pr)(*s*-Bu)	54	S(*n*-Pr)(*n*-Bu)	62	S(*n*-Bu)(*t*-Bu)	69
S(*i*-Bu)(*s*-Bu)	55	S(*n*-Bu)$_2$	63	S(*n*-Pr)Bn[a]	69
S(*n*-Bu)(*s*-Bu)	56	S(*n*-Pr)(*i*-Bu)	63	S(*i*-Bu)(*t*-Bu)	70
SEt$_2$	58	S(*s*-Bu)Bn[a]	63	S(*n*-Bu)Bn[a]	70
S(*s*-Bu)(*t*-Bu)	58	S(*i*-Pr)Bn[a]	64	S(*t*-Bu)Bn[a]	76
SMeBn[a]	59	S(*n*-Bu)(*i*-Bu)	64	S(*t*-Bu)$_2$	85
SMe(*t*-Bu)	59	S(*i*-Bu)$_2$	65		

[a] Bn = benzyl, CH_2Ph.
[b] Cy = cyclohexyl.

from the least-squared line as the number of conformational degrees of freedom increased in the ligand. It is likely that the conformations chosen by Brown et al. and those used in this study are different due to different conformational search strategies.

In the original ligand repulsive energy study, a few hundred conformations were generated with partial minimization (typically 300 steps of minimization using the conjugate gradient minimizer with termination criterion of 0.1 kcal/mol·Å).[4, 12, 13] In this study a much more rigorous, albeit not exhaustive, conformational search was performed (2000 conformers were generated with the SMART minimizer). (We should note that the conjugate gradient minimizer is a first-derivative minimizer,

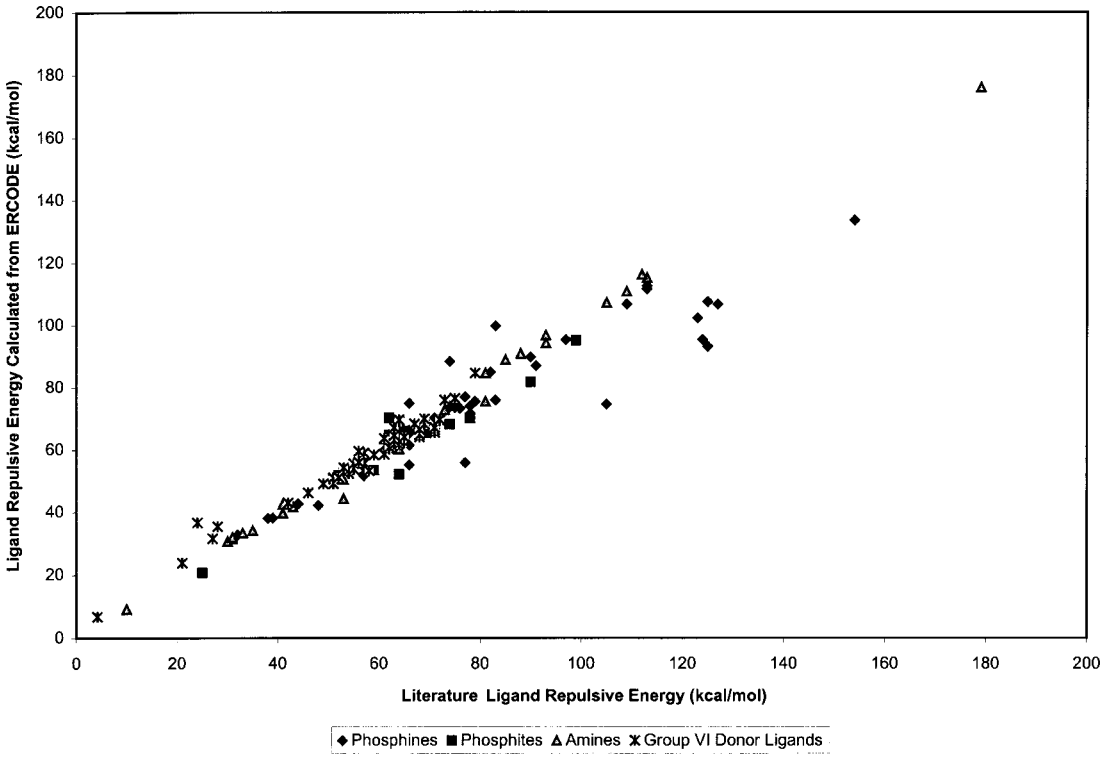

FIGURE 1. Plot of ligand repulsive energy calculated from *ERCODE* against literature E_R values.[4, 12, 13] Outliers are discussed in the text.

whereas the SMART minimizer uses a combination of the conjugate gradient and Newton–Raphson methods.[8]) One significant outlier found in this study was triphenyl phosphite, $P(OPh)_3$, which has a reported $E_R = 66$ kcal/mol,[4] whereas *ERCODE* gives $E_R = 87$ kcal/mol (Table I). We found several structurally reasonable conformers of $P(OPh)_3$ with $E_R = 66$ kcal/mol, computed with *ERCODE*. However, each of these conformers was of higher energy than the structure that yielded $E_R = 87$ kcal/mol. It appears as though our lowest energy conformer has one of the phenyl groups fanned out to relieve intraligand repulsion. This fanning causes increased repulsion between phenyl rings and basal carbonyl groups in the $Cr(CO)_5$ fragment as the Cr—P bond is varied in the calculation of E_R (Fig. 2a). Higher energy conformers have the phenyl rings folded back so there is less repulsion between phenyl rings and basal CO groups. The result is a lower E_R value, but greater intraligand repulsion between the phenyl groups in the $P(OPh)_3$, resulting in a higher total molecular mechanics energy (Fig. 2b) for the free ligand. In essence, we note that the lower energy conformer has a higher ligand repulsive energy, suggesting a lack of correlation between steric bulk and total molecular mechanics energy, also noted by Brown.[4] Some, less dramatic outliers were noted as well; and all these cases involved ligands with many conformational degrees of freedom.

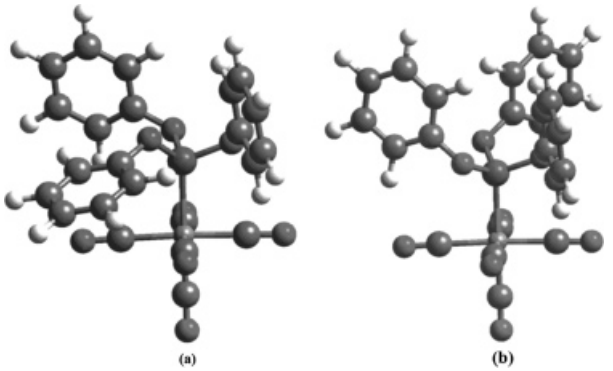

FIGURE 2. Structures for $[Cr(CO)_5\{P(OPh)_3\}]$. (a) Shows the lowest energy structure with total molecular mechanics energy, $E_{tot} = -2.35$ kcal/mol and $E_R = 87$ kcal/mol. (b) Shows the next lowest energy structure with $E_{tot} = -1.65$ kcal/mol and $E_R = 66$ kcal/mol. Notice how one phenyl ring in (a) is tilted towards the basal CO groups, relieving the intraligand repulsion but increasing the ligand repulsive energy. In (b), all three phenyl groups are pointed away from the basal CO groups, giving rise to a much lower E_R value, but a slightly higher total molecular mechanics energy.

Many linear free energy relationships (LFER) involving steric effects contain scatter.[6,7] In a chemical reaction involving a ligand with many conformational degrees of freedom, there is always an ensemble of conformers of the ligand in solution. However, most measures of steric size only take into account one conformation of the ligand.[5–7] In the case of Tolman's cone angle, the conformation that gave rise to the smallest cone angle was used.[2,5] In the case of the solid-angle and ligand-repulsive energy, the lowest energy structure in a conformational search was used.[3,4] Mosbo and coworkers suggested using Boltzmann weighted cone angles to overcome the problem of multiple conformations solution.[18,19] The significant difference in ligand-repulsive energy between the lowest energy form of $P(OPh)_3$ ($E_R = 87$ kcal/mol) and a low energy form only 0.70 kcal/mol higher in energy ($E_R = 66$ kcal/mol) suggests the need to consider a Boltzmann weighted set of ligand repulsive energies as likely to be more representative of the effective steric requirement of the ligand. In solution, these two conformers will compete for binding to a reaction center. A substrate that is sensitive to the ligand steric requirement will readily accommodate a ligand in a conformation with lower E_R value, with the difference in binding energy more than compensating for the difference in energies of the free ligand conformers. Use of a weighted E_R value, which would yield a value smaller than 87 kcal/mol, would provide a better estimate of the steric requirements of the ligand. Employment of an energy-weighted steric parameter could significantly reduce the scatter observed in LFER plots. Work to determine the feasibility of this approach is underway in our laboratories.

Conclusions

We have presented a new code, *ERCODE* (see Supplementary Material), to efficiently calculate steric sizes of ligands. We have provided examples of the calculation of ligand repulsive energy for 192 different ligands. Many of these values are updated from those that appear in the literature.[4,6,7,12,13] *ERCODE* can be used to calculate steric sizes of any ligand in any prototypical environment as long as a representative structure is found, the file converted into a bgf type, and appropriate van der Waals parameters are defined.

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